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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/215,163	12/18/98	STINSON J	04995.0032-0

EXAMINER	
GRASER, J	
ART UNIT	PAPER NUMBER
1645	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/215,163	Stinson et al.
Examiner	**Art Unit**
Graser, Jennifer	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Amendment B, 3/14/2001*.

2a) [X] This action is **FINAL.** 2b) [ ] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1-31* is/are pending in the application.

4a) Of the above, claim(s) *3-12, 21, 22, 24-28, 30, and 31* is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *1, 2, 13-20, 23, and 29* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) [X] Notice of References Cited (PTO-892)
16) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) [ ] Interview Summary (PTO-413) Paper No(s). _____
19) [ ] Notice of Informal Patent Application (PTO-152)
20) [ ] Other:

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

1. Acknowledgment and entry of the Amendment submitted 3/14/01, Paper No. 11B is made. Claims 1, 2, 13-20, 23 and 29 are currently under examination.

This application contains claims 3-12, 21, 22, 24-28, 30 and 31 drawn to a non-elected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

2. Claims 23 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23 and 29 are vague and indefinite due to the phrase "or fragment or derivative thereof". The term "derivative" does not provide the character or properties from the source that are to be retained in the final product, e.g., paper is derived from wood but is very different from wood. Additionally, the terms "derivative" and "fragment" imply no functionality, i.e, their is no epitope binding region retained. Further, the terms read on as little as one amino acid.

Applicants have argued that 'derivatives' refer to antibodies with modifications such as deletions, substitutions, or additions to the amino acid sequence that do not appreciable diminish the characteristic binding associated with the exemplified variable regions. This has been fully and

carefully considered but is not deemed persuasive. The term 'derivative' in and of itself do not provide the structural properties which are to be retained in the final product. This claim does not require an epitope to be retained, but is merely a fragment or derivative of an antibody which binds Shiga toxin. Additionally, see the 112, first paragraph enablement rejection which teaches that it is extremely unpredictable to change amino acids in a give amino acid sequence and retain function. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. Claims 1, 13-20, 23 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a humanized monoclonal antibody which binds to Shiga toxin I, does not reasonably provide enablement for 'humanized monoclonal antibodies which bind to Shiga toxin type 1 variants' or 'fragments or derivatives' from a humanized monoclonal antibody which binds to Shiga toxin type 1, nor does the specification enabled for humanized monoclonal antibodies wherein 'at least part of' the variable region is from SEQ ID NO:42 and SEQ ID NO:43. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 23 and 29 recite fragments or derivatives from a humanized monoclonal antibody yet provide no functional and/or size limitation. These fragments and derivatives do not have to have a use, i.e., they may not necessarily bind Shiga Toxin 1. The specification further discloses humanized monoclonal antibodies which will bind to Shiga type I toxin and humanized

monoclonal antibodies which contain "at least part of the variable region from SEQ ID NO:42 and 43. The specification states that substitutions, additions, or deletions may be made to the sequence encoding the antibody; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the antibody to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spacial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. The changes allowed for in the claims could cause a detrimental effect to the antibody to be produced and could cause total negation of any epitopes which could correctly bind Shiga Toxin I. It is unclear that an immunogenic epitope binding region would be retained in the fragments and derivatives. Additionally, the specification has not adequately set forth the location of immunoprotective epitopes. The specification sets forth nothing less than a humanized monoclonal antibody which can bind Shiga Toxin I as exemplified the deposits recited in claim 2. Selective point mutation to one key antigen residue could, in practical terms, eliminate the ability of the antibody to recognize the Shiga I toxin. If the range of decreased binding ability after single point mutation of an antibody varies, one could expect point mutations in the antibody to cause varying degrees of loss

of binding, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes could result in a complete loss of binding. An antibody having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antibody that is precipitously or progressively unrecognizable and unable to bind to the Shiga toxin. Thus, antibodies of different levels of homology may not recognize by the native Shiga Toxin I. Given the lack of guidance contained in the specification and the unpredictability for determining acceptable amino acid substitutions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation..

Additionally, claim 2 recites humanized monoclonal antibodies having the same binding specificity as three deposited monoclonal antibodies. Applicants argued in the former Office Action that a deposit of these ATCC antibodies was not required because they were publicly known and available as evidenced by the prior art relied upon in the 35 USC 103 rejection. This was persuasive with respect to the deposited antibodies. However, claim 2 is drawn to antibodies with the same binding specificity as the deposited antibodies. According to prior art references, monoclonal antibodies can be readily produced; however, the total characterization of a monoclonal antibody is a long and complex procedure which varies widely with the intended use of the antibody. A general point is that if a single hybridoma has been produced and is intended for a specific function it is *unlikely* that the antibody produced will have all the required characteristics (Campbell, Laboratory Techniques, Vol. 13, 1984). Campbell teaches that it is a

waste of both reagents and time to attempt full characterization of an antibody which is not obtained from a fully cloned cell line. See Chapter 10, specifically page 186. While the specification provides enough information for one of ordinary skill in the art to produce hybridoma cell lines secreting antibodies with similar properties as monoclonal antibodies 13C4, and 11E10, reproduction of an identical cell line and antibody is an extremely unpredictable event (see Campbell above). Accordingly, it would take one of skill in the art undue experimentation to produce humanized antibodies with the identical binding specificity as the deposited antibodies of claim 2.

Claim Rejections - 35 USC § 103

4. Claims 1, 2, 13-20, 23 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Speirs et al (Can. J. Microbiol., 1991, 37: 650-653) or O'Brien et al (US 5,747,272) in view of Shitara et al (US 5,866,692).

Speirs et al teach the 11E10 monoclonal antibody which binds to shiga-toxin II. See especially abstract, page 651, first column).

O'Brien et al also teach the 11E10 monoclonal antibody of the IgG1 subclass with a kappa light chain. See especially column 4, lines 38-58.

Shitara et al teach a method of producing humanized chimera antibodies. Humanized chimera does not cause formation of anti-mouse immunoglobulin antibody in the body of the patient and therefore side effects are reduced. See abstract and column 1, lines 10-48).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to synthesize and express the humanized chimera antibody which binds to the shiga-like toxin type II. One of ordinary skill in the art would have been motivated to humanize the monoclonal antibodies taught by Speirs and O'Brien because doing so would avoid the side effects caused by anti-mouse immunoglobulin antibody when monoclonal antibody is administered, yet it would still maintain an effective therapeutic effect. The humanization of a monoclonal antibody which is already known in the prior art, particularly one directed to a human pathogen, would have been obvious at the time the invention was made since it was a common procedure to allow for the passive immunization against human pathogens while avoiding serious side effects.

Response to Applicants' arguments:

Applicants have argued that just because a technique is common does not necessarily create a motivation to combine it with another technique or reagent. They argue that even if humanizing monoclonal antibodies is a common technique, this does not suggest that all monoclonal antibodies, whether directed to human pathogens or not, should be humanized. This has been fully considered but is not deemed persuasive. It is maintained that the humanization of a monoclonal antibody which is already known in the prior art, particularly one directed to a human pathogen, would have been obvious at the time the invention was made since it was a common procedure to allow for the passive immunization against human pathogens while avoiding serious side effects.

Applicants cite the abstract of Iwahashi et al which describes the humanization of a murine monoclonal antibody. They argue that this abstract is an example that humanization of antibodies does not necessarily circumvent the problem of immunogenicity that humanizing tries to overcome. This has been fully and carefully considered, but is not deemed persuasive. Iwahashi et al demonstrate that those of ordinary skill in the art routinely humanize monoclonal antibodies to determine their clinical potential. This reference supports the rejection of record. Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. However, Iwahashi et al does provide absolute success with regard to the humanization of a monoclonal antibody. The current invention is drawn to a product, not a method. The prior art teaches that it would have been obvious to make this product. Applicants' arguments with respect to Merluzzi et al have been considered but are not deemed persuasive.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Status of Claims

6. No claims are allowed.

7. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

J Graser 5/7/01

Jennifer Graser
Primary Examiner
Art Unit 1645